

Bayer HealthCare
Bayer Schering Pharma



SCIENCE FOR A BETTER LIFE – FROM MOLECULES TO MEDICINE

A journey through research and development



Science For A Better Life – From molecules to medicine

Bayer Schering Pharma invests considerable resources in the research and development of new drugs, with the aim of improving patients' quality of life and prolonging lives. We focus on therapeutic areas with a high unmet medical need, areas that require further innovation despite the progress that has been made – as for example in cancer therapy.

It takes about twelve years to develop a new drug. During this time, highly qualified scientists from a variety of disciplines work on filtering out a suitable active ingredient from an enormous number of compounds. They study 5,000 to 10,000 compounds, of which only four or five drug candidates eventually remain. These are then tested on humans in clinical studies. At the end of the process, only one substance is approved and becomes available to physicians and patients. Cooperation in interdepartmental, multidisciplinary teams is an important requirement for success in the complex process of drug development.

With this brochure, we cordially invite you to join us on a tour of our research departments to gain an insight into the work of our scientists. In ten chapters you can follow a new drug as it develops from a molecule to a medicine.



A handwritten signature in black ink, appearing to read 'A. Busch'.

Prof. Dr. Andreas Busch
Head of Global Drug Discovery
Bayer Schering Pharma

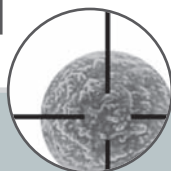


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Dr. Kemal Malik
Head of Global Development
Bayer Schering Pharma

Finding the right approach – Target Discovery

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The development of every drug begins with the search for a target on which the drug can act. To find one, researchers need to have very precise knowledge of the biochemical processes that take place in the body and how these are changed by a disease.

The scientists focus their attention on the signaling pathways of cells which control all the body's major functions. Understanding these biochemical processes in the body can yield valuable clues as to how a disease can be combated. This is because the signaling cascades involve proteins that can be potential sites of action for drugs. These target sites are usually receptors – cellular binding sites for hormones and other messengers – or enzymes, which are responsible for the chemical transformation of substances in the body. Drugs either switch these proteins off or enhance their function. However, only few protein molecules are suitable as targets for drugs. It is a difficult and complex task to detect them among the countless proteins that are produced by the body.

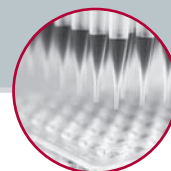
Proteins that might be playing a significant role in the course of a disease can be identified using DNA chips. This is done by detecting messenger RNA (mRNA). The scientists use RNA interference to establish whether these proteins are suitable as targets. This method makes it possible to switch off individual genes by the targeted degradation of their mRNA. As mRNAs code for proteins, any target protein can be switched off in this way. If the disease-specific process at the cellular level subsequently changes, this suggests that the blocked protein might be a suitable drug target. Careful work is very important at this stage of the research process, since the quality of a target is key to the success of the subsequent work steps.



Disease-related proteins can be identified using DNA chip technology.

Looking for the needle in the haystack – High-Throughput Screening (HTS)

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Once a target has been successfully identified, the scientists use a systematic test procedure to look for substances – known as lead candidates – which could be a suitable starting point for a new active ingredient. They must be able to bind well to the target protein; i.e. they must fit into the target like a key into a lock.

To find these potential active compounds, the researchers first develop detection tests matched to the respected target that are suitable for use in the automated and miniaturized process. They then use high throughput screening (HTS) to comb through the in-house compound library (currently containing over two million chemical substances) for suitable lead candidates. Robots fill thousands of microtiter plates on which up to 1536 tests can be performed simultaneously. In this way, the target is automatically mixed with quantities of the substances as minute as 50 nanoliters. Since HTS ensures a very high test throughput, this process only takes a few weeks.

The scientists use various detecting procedures to measure the effect on the target after binding a compound. They often use highly sensitive CCD cameras to gather fluorescent light released after a substance has bound to a target protein. A computer-assisted evaluation of the quantity of light then identifies the compounds that have the desired effect.

The researchers determine the potency of the most interesting compounds by testing them in dilution series. Finally, they further examine the sufficiently potent candidates for undesirable (side) effects. The lead candidates that have now been found are not yet ready for use, however. They have to be optimized in further stages of the development process.



Minute amounts of substances are prepared in microtiter plates by robots.

Modeling molecules – Structural biology / Computational Chemistry

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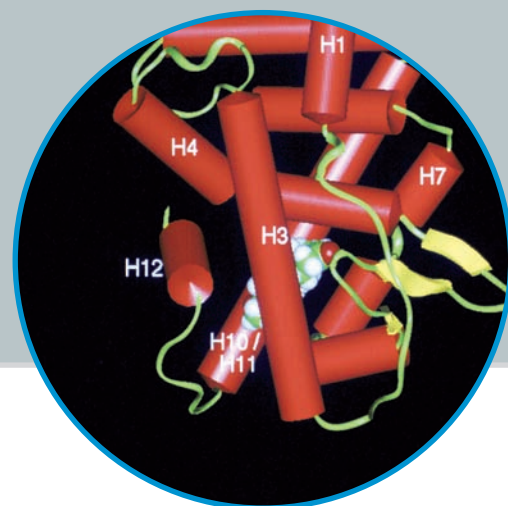
In addition to compound screening, computer-based methods are used to find and develop suitable drug candidates. Computational chemistry can only be used if the exact molecular structure of the target proteins is known.

Structural biologists determine the molecular properties of the targets. They investigate the position of pockets to which the active compounds can bind and the interaction between these protein pockets and the active substance. For this purpose they use X-ray structural analysis, which only can be performed on crystallized target proteins. However, the generally lengthy crystallization process does not succeed with every protein. The lattice structure of the crystallized protein diffracts the X-ray beam in a characteristic way. Structural biologists can read the electron density and thus the position of the atoms from the diffraction pattern. In this way they can draw conclusions on the molecular structure.

Computational chemists use this information to find further substances that fit the binding pockets of the target proteins. To do this, they use computerized screening processes to search through virtual compound libraries. In this way they can identify molecules that have not yet been synthesized and others that can be purchased from external vendors. The subsequent stage of lead optimization also benefits from computational chemistry.

Computer calculations can thus be used not only to predict which molecular modifications of a substance are likely to improve its capacity to bind to the target, but also which biophysical or toxic properties might be associated with a structural transformation.

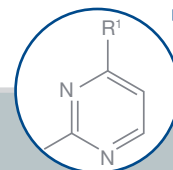
This enables the synthetic chemists to do their work in the laboratory in a more targeted manner. However, the natural flexibility of protein structures makes reliable predictions difficult – ultimately, it is always the experiment actually conducted that counts.



Progesterone receptor model.

Finding the optimum – Medicinal chemistry

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The compounds identified up to now do not yet have all the properties of an active ingredient. At this stage they might be compared with key blanks that can be inserted into the lock, but not turned. Medicinal chemistry gives them the finishing they need.

In addition to having the desired effect, a substance must meet other criteria. If possible, it should bind only to the target and not to other molecules in the body to minimize adverse effects. It must not break down before it has a chance to have its effect, and it must be soluble in water to get into the body at all.

In order to create molecules with such properties, chemists vary the lead candidates by adding or removing various chemical groups or by modifying the molecular structure. They first systematically create hundreds or even thousands of different variations using automated processes (automated medicinal chemistry). These are then further screened to filter out candidates that are most likely to meet the requirements. This process is supported by computer simulations. These improved lead compounds are then subjected to repeated biological tests. These give the medicinal chemists ideas for further optimization steps.

The alternating process of chemical optimization and testing usually takes several years. Researchers often make hundreds of modifications to a lead compound in the course of its development. The experience of medicinal chemists is very important in this work. When they improve one desired property of a molecule, this sometimes worsen others. When the scientists are finally convinced that they have found a compound that exhibits the desired properties, they apply for a patent. Preclinical development can now begin.



Scientist monitoring
a synthesis robot.

Understanding effects – Pharmacology and toxicology

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At the preclinical development stage, pharmacologists and toxicologists test the new active compound under experimental conditions. They study the desired and adverse effects of the new drug candidate with the aim of determining in detail how it will react in the body.

Pharmacology is divided into pharmacodynamics and pharmacokinetics. Pharmacodynamics investigates whether the compound's already proven binding capacity to the target molecule has a physiological effect, i.e. whether the active compound really is capable of treating the disease. Pharmacokinetics studies the absorption, distribution, metabolism and excretion of a drug. It can therefore happen that an active compound is prematurely broken down in the stomach or liver and never reaches its true destination, or even that metabolism converts it into a toxic substance. Such knowledge is indispensable for developing a form of administration. Toxicologists investigate whether the substance has a toxic effect on the body and whether it is capable of causing cancer, genetic mutations or damage to unborn children. The dose is critically important here. Pharmacologists and toxicologists therefore determine what is known as the therapeutic window. This is the span between the minimum dose at which a therapeutic effect becomes just visible and the maximum dose at which there is no toxic effect.

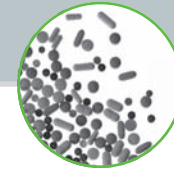
The scientists in preclinical development have three courses of action at their disposal. First they use computer programs – in silico – to simulate processes to dismiss any unsuitable candidates. They subsequently test the active compounds in test tubes or Petri dishes – in vitro – on cell and tissue cultures or with bacteria. Finally, animal experiments – in vivo – are vital to understanding the complex interactions that take place in an entire organism. These studies are required by law and are governed by strict guidelines and state controls.



At the preclinical development stage, pharmacologists and toxicologists test the new active substances under various conditions.

Packaging the active ingredient – Galenics

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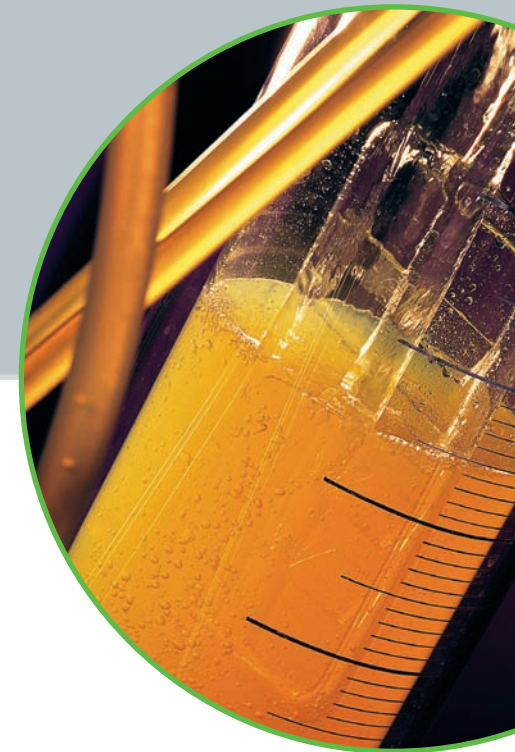


An active ingredient still has a long way to go before it becomes a drug. It has to be incorporated into a suitable form of administration so that it can be transported to the part of the body where it is needed. Galenics is the science that turns an active ingredient into a safe, ready-to-use product that can be dosed as required.

Factors to be considered in the development of a suitable form of administration — be it a tablet, an ointment or a patch — include patient acceptance and the specific requirements of the active ingredient. Inactive ingredients making up most of a drug's volume serve as carriers for the active compound. Maize starch or lactose, for example, are used in tablets, while water-oil emulsions are used in ointments.

The administration form influences a drug's therapeutic effect. It determines how the active ingredient enters the body, where and in what dosage it is released, and the time it takes to be absorbed. For example, compounds that need to be released into the body slowly and continuously can be incorporated into additives that are not readily soluble. Active ingredients that would not survive passage through the liver are transported directly into the blood circuit via patch or injections. In addition, the mode of administration must ensure that the patient will be able to dose the drug safely and handle it easily.

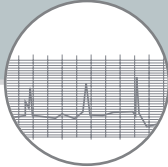
Galenics experts are also responsible for a drug's storage safety. They ensure that the active ingredient's content remains constant, the product remains chemically stable throughout its shelf life, and that it maintains its purity. Another requirement is that the formulation can be manufactured on an industrial scale. Beginning with a prototype, the next step is to reproduce it on a laboratory scale. By scaling up production in several steps at the test facility, the scientists finally reach large-scale production. The newly developed drug formulation is initially used and tested in clinical trials before it reaches the market as an approved drug.



Production of liposomes as a vehicle for drug substance transport in the human body.

Testing tolerability – Phase I of clinical development

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Phase I clinical trials are the first stage at which physicians study the active ingredient in humans. They test its safety and tolerability as well as the way it affects the body. These studies are usually conducted on small groups of healthy volunteers.

The studies are usually conducted at study centers operated by the drug's manufacturer. Quite a small number of volunteers are initially given a very small quantity of the active ingredient. The dose is then gradually increased in different volunteers until the maximum tolerable dose has been identified. In this process, physicians monitor blood parameters and other vital signs such as blood pressure, heart rate and ECG to determine the side effects.

They use blood, urine and stool samples to determine how a compound is absorbed, distributed, metabolized and excreted by the human body. In further studies, the physicians monitor interactions with other drugs or nutritional substances. Finally, they investigate how the new medication can be most effectively administered — a prerequisite for enabling the pharmacists to find a final formulation for the active ingredient.

The participants are comprehensively briefed beforehand about the planned study and possible risks. They give their written consent to participate, but can later revoke it at any time. They receive an expense allowance for their participation. All clinical trials involving humans are governed by strict scientific and ethical principles. A study protocol describes what is to be studied, how the trial is to be conducted, and why it is necessary. These study protocols have to be approved by the regulatory authority and an independent ethics commission. If a drug proves to be well tolerated in Phase I, it will then be tested in the now following Phases II and III on patients who are suffering from the respective disease.

A physician performs a health check with a study participant.



Confirming efficacy – Phases II and III of clinical development

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In clinical trials, large patient groups are studied by physicians to determine the efficacy and safety of the new drug candidate. Independent hospitals or physicians' practices in many countries are involved in this phase of clinical development.

The drug candidate with the new active ingredient is tested in two steps. Between 100 and 500 patients initially take part in Phase II studies. In Phase III, investigators test the drug on as many as several thousand patients. They examine whether the tested drug candidate is effective and, if so, to what degree, as well as which dosage is optimal for treatment and how often adverse events appear. Here, too, patients must give their consent to take part in the study.

The physicians compare the new active ingredient with an established form of therapy or with placebos – an inactive substance containing no medication – to exclude any distortion of the clinical results as far as possible. The patients are assigned by lots to one group or the other. They do not know which group they belong to, because their expectations might influence the results. If neither the physicians nor the study participants know which preparation is being used, the study is called double-blind study. Only after the study is completed all participants are informed about their respective treatment group.

The physicians taking part in a clinical trial meticulously document the treatments, measurements and results, and pass the data on to the pharmaceutical manufacturer in anonymized form. The manufacturer uses sophisticated database systems to handle and statistically analyze the enormous volume of data. The interpretation of the data ultimately shows whether the results are medically relevant and it is worthwhile applying for the drug's approval. Clinical development brings a logistically extremely complex, lengthy and cost-intensive process to a close. The trials, which take four to eight years, account for over half a drug's total development costs.



Study physicians carefully document all trial data.

Individually predicting effects – Pharmacogenomics



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Drugs often have a variable effect. The science of pharmacogenomics analyzes the interaction between people's genetic make-up and their reaction to drugs with the aim of developing customized therapies for patients in the future.

A person's genetic disposition influences the absorption, metabolism and effect of a drug in the body. These processes are governed by certain protein molecules such as enzymes and receptors. The information stored in our genetic material (DNA) provides the blueprint for these proteins. Inherited variations in the sequence of an individual's DNA building blocks – called single nucleotide polymorphisms or SNPs – can influence whether certain protein molecules are present or missing and affect their activity. Scientists use systems called microarrays to study these genetic characteristics, which are specific to individuals, and gene expression. They allow more than a million gene variations to be examined simultaneously.

Pharmacogenomics offers the future promise of treatments in which the active ingredient and the dosage are tailored to the individual patient's needs. In this way, the maximum possible therapeutic success could be achieved with a minimum of adverse effects. Treatment costs could also be reduced. Test procedures are already available which enable scientists to make reasonable predictions on whether individual drugs will have a desired effect on a patient. Pharmacogenomic advances also make clinical trials simpler, cheaper and safer, because they make it possible to recruit study participants in a targeted manner – patients who are highly likely to respond to the compound to be tested and unlikely to suffer serious adverse effects.

Using genetic data raises ethical and legal issues. For researched-based pharmaceutical companies, sensitive handling of genetic information and compliance with strict data-protection regulations form the basis of their scientific work.

More than one million genetic variations can be analyzed simultaneously using gene chips.

Putting it all together – Regulatory Affairs

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Drugs may only be launched if they have been given regulatory approval. The Regulatory Affairs department is responsible for preparing this final step of drug development. This department compiles the dossier that is submitted to the regulatory authorities and is their contact office.

The documentation submitted to a regulatory agency by the pharmaceutical company contains all the data generated during the development and test phases. This dossier with the results from chemical-pharmaceutical, toxicological and clinical trials can fill several hundred files. The agency reviews the documentation to see whether it provides sufficient evidence to prove the efficacy, safety and quality of the drug for the proposed indication.

The Regulatory Affairs staff are also involved earlier, during a drug's development process. They ensure that, wherever possible, all the necessary steps for approval are considered already at an early stage. Indeed, most drugs achieve approval in this way, although in some cases it is subject to conditions, e.g. restricting the number of indications or requiring warning notices.

As a rule, pharmaceutical companies strive to market their products worldwide. To do so, they require approval for each individual country. This is granted in Germany by the Federal Institute for Drugs and Medical Devices, in the USA by the Food and Drug Administration (FDA). In the European Union, the EMA is responsible for central approval, which is valid for all member states. Pharmaceutical manufacturers usually first apply for approval in the USA and Europe. If it is granted there, they also apply in the remaining countries. A simplified procedure is then generally sufficient. Approval marks the successful completion of a long process.

After a development process lasting eight to ten years, and a global approval process lasting three to five years, the drug is finally available to patients all over the world.

Masthead

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